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<b>(21) International Application Number:</b> PCT/US93/11732 <b>(22) International Filing Date:</b> 3 December 1993 (03.12.93)  <b>(30) Priority Data:</b> 07/986,959 9 December 1992 (09.12.92) US  <b>(71) Applicant:</b> ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 92713-9534, Irvine, CA 92713-9534 (US).  <b>(72) Inventors:</b> POWELL, Charles, Hayes; 20 Tangelo Street, Irvine, CA 92720 (US). KARAGEOZIAN, Hampar; 31021 Marbella Vista, San Juan Capistrano, CA 92675 (US). CURRIE, James, P.; 28746 Vista Santiago Road, Trabuco Canyon, CA 92679 (US).  <b>(74) Agents:</b> VOET, Martin, A. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).		<b>(81) Designated States:</b> AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> CLEANING COMPOSITIONS AND METHOD FOR HYDROPHILIC CONTACT LENSES  <b>(57) Abstract</b>  Disclosed are compositions and methods for inhibiting the uptake of proteins and reducing the formation of lysozyme deposits on the outer surface and inner bulk matrix of hydrophilic contact lenses. One method comprises contacting a contact lens with a chemical agent selected from the group consisting of protamines, polyarginine, polylysine, chitosan and mixtures thereof. Another method comprises placing the lens in a hypotonic solution for a period of time sufficient to cause the lens to swell and the pores of the matrix to expand. A negatively charged chemical agent selected from the group consisting of chloride salts, chlorite salts, ethylenediaminetetraacetic acid sodium salts, cysteine salts and mixtures thereof is then added to the solution such that the osmotic pressure of the solution causes the lens and its pores to constrict to their normal size. The chemical agent is also present in an amount sufficient to cause desorption of the protein deposits from the surface and matrix of the lens. Subsequently, the lens is soaked in the solution having the chemical agent for a period of time to appreciably reduce and/or inhibit the formation of protein deposits on and/or in the lens. Another method of this invention comprises contacting a contact lens with a high molecular weight, negatively charged chemical agent selected from the group consisting of, for example, alginic acid, xanthan gum and mixtures thereof.		

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Cleaning compositions and methods for hydrophilic  
contact lenses

**Field of the Invention**

5           This invention relates generally to cleaning contact lenses. More particularly, the present invention relates to compositions and methods useful for inhibiting the uptake of proteins and reducing the formation of protein deposits on the outer surface and/or in the inner bulk matrix of hydrophilic contact lenses.

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**Background of the Invention**

          During handling and wear, contact lenses are susceptible to the accumulation of a variety of materials which may adhere to the surface of the lens and/or lodge within and adhere both chemically and/or spatially to the  
15           inner bulk matrix of the lens. For example, during wear, lenses contact proteinaceous materials such as lysozyme and mucoproteins, both of which are constituents of lachrymal tears, and lipids such as sterols, waxes, glycerides, phospholipids, fatty alcohols and acids.

          If contact lenses are not properly cleaned, lysozyme, mucoproteins and  
20           other soils can accumulate on and/or in the lens to a point where the lens wearer begins to feel discomfort, the lens spectral characteristics are adversely affected, sterilization becomes difficult and/or the gas permeability may be decreased.

          Certain types of cleaning or disinfecting techniques and compositions  
25           have been found inadequate for inhibiting and reducing the formation of these deposits on hydrophilic contact lenses. For example, it has been shown that sterilization techniques such as heat in the form of boiling water or steam can have adverse effects on soft lenses. High temperatures may cause tear proteins to be baked onto the contact lens polymer, resulting in difficulties in  
30           cleaning. Heat sterilization techniques also tend to accelerate lens buildup by precipitating absorbed proteinaceous materials. Sterile saline solutions have limited effect on the removal of soils, thus, requiring some additional cleaning

procedure. Peroxides, which are effective disinfectants against ocular pathogens, have also been found to be inadequate for removing lens soils.

Attempts have been made to reduce and inhibit the tendency for proteins to adhere to a lens surface. For example, U.S. Patent No. 4,168,112 to Ellis  
5 discloses forming a thin ionic polymeric coating on a contact lens having an ionically charged surface. The coating is electrostatically bound to the lens surface and reduces the tendency for mucoproteins to adhere to the lens surface. Ellis shows contact lens solutions containing cationic polymers for forming a hydrophilic polyelectrolytic complex on the lens surface wherein the  
10 complex acts as a hydrogel "cushion." Other additives to the lens solutions shown by Ellis include preservatives such as ethylenediaminetetraacetic acid (EDTA).

U.S. Patent No. 4,414,127 to Fu discloses compositions which degrade and remove proteinaceous deposits from all types of contact lens plastics by  
15 chemically degrading these deposits into water-soluble proteins. Fu shows using metal chloride salts as catalysts for peroxide decomposition where the peroxide is used in a contact lens cleaning solution.

U.S. Patent No. 4,259,202 to Tanaka discloses a solution used for cleaning and preserving contact lenses. The solution of Tanaka contains as an  
20 effective ingredient a particular monoester of saccharose with a fatty acid. The solution also contains an alkali metal salt of a saturated fatty acid and a compound selected from the group consisting of a polysaccharide and a polysaccharide derivative. Examples of the polysaccharide and its derivative include alkali metal salt of alginic acid, xanthan gum, alkali metal salt of  
25 carboxymethyl cellulose, hydroxypropyl methylcellulose and alkali metal salt of chondroitin sulfuric acid.

Bendazac lysine, an anti-cataract drug, has been found to limit protein deposition on soft contact lenses. See Missiroli, A., Ricci, F., Pocobelli, A., Cedrone, C., Cerulli, L., CLAO Journal (Contact Lens Association of  
30 Ophthalmologists), April 1991, 17(2) pp. 126-8. Bendazac lysine is an oxyacetic acid with known anti-inflammatory, antinecrotic, choleretic and antilipidaemic properties, but it is said that its principal effect is to inhibit the denaturation of proteins.

There continues to be a need for a system capable of effectively reducing,  
35 inhibiting and reversing the deposition of proteins, not only from the surface of a contact lens, but also from the inner bulk matrix of the lens. The

accumulation of these proteins in the inner bulk matrix may cause discomfort to the wearer, adversely affect the lens spectral characteristics, decrease lens oxygen permeability and decrease the overall estimated useful lifetime of the lens.

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#### **Summary of the Invention**

The present invention is directed to ophthalmically safe compositions and methods for cleaning contact lenses, and more specifically to compositions and methods used as in-the-eye and/or out-of-eye inhibitors and reversers of surface and/or inner bulk matrix deposition of lysozyme on hydrophilic contact lenses.

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In one aspect of the present invention, the formation of protein deposits on the surface and/or in the inner bulk matrix is reduced and/or inhibited by contacting a contact lens with a chemical agent selected from the group consisting of basic peptides, such as protamine, polyarginine or polylysine and/or basic polymeric carbohydrates, such as chitosan, and mixtures thereof.

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In another aspect, the present invention is directed to a method of inhibiting the uptake of proteins and reversing the formation of protein deposits on hydrophilic contact lenses. The method comprises the steps of placing a contact lens in a hypotonic solution for a period of time sufficient to cause the lens to swell and the pores of the matrix to expand. Subsequently, a negatively charged chemical agent is added to the solution in an amount sufficient to change the tonicity of the solution in order to cause the lens and the pores to constrict, while also facilitating desorption of protein deposits from the surface and matrix of the lens. The chemical agent is selected from the group consisting of chloride salts, chlorite salts, ethylenediaminetetraacetic acid, cysteine and mixtures thereof. The lens is soaked in the solution having the chemical agent for a period of time sufficient to substantially reduce and/or inhibit the formation of protein deposits on and/or in the lens.

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In yet another aspect of the present invention, a contact lens is contacted with a solution comprising a negatively charged chemical agent selected from the group consisting of alginic acid, xanthan gum, other high molecular weight ionic carbohydrates and mixtures thereof, for a period of time such that the chemical agent facilitates desorption of the proteins.

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The foregoing and other objects, features and advantages of the present invention will become more readily apparent from the following detailed description.

**Description of the Invention**

The present invention is directed to the use of various chemical agents as in-the-eye and/or out-of-eye inhibitors and reversers of surface and inner bulk matrix deposition of lysozyme on hydrophilic contact lenses. The present invention is also directed to methods for inhibiting and/or reducing the formation of protein deposits on the surface and/or in the matrix of hydrophilic contact lenses.

While the present invention can be used in connection with a variety of contact lenses, it is preferred that the contact lenses used with the present invention are hydrophilic lenses comprising methacrylic acid as a copolymer. Group III and Group IV lenses are examples of such lenses.

In one embodiment, the present invention involves a method of inhibiting the uptake of proteins and/or appreciably reducing the formation of tear protein deposits on the outer surface and/or in the inner bulk matrix of a hydrophilic contact lens. This method comprises contacting a contact lens with a chemical agent that is positively charged (at physiological pH's 7 to 8), oligomeric and water soluble. It is preferably selected from the group consisting of protamines, polyarginine, polylysine, chitosan, chitosan salts such as chitosan hydrochloride, chitosan derivatives such as chitosan biguanide and mixtures thereof.

For purposes of this invention the term "appreciably" generally means that the lens is more comfortable to the lens wearer and the amount of proteins adhering to the lens is noticeably decreased with the assistance of a 10x magnifier. More specifically, appreciably means the amount of proteins deposited on the lens is preferably reduced by about 40%, more preferably about 40% to about 75%, and even more preferably about 75% to about 95%.

For purposes of this aspect of the present invention, protamines are defined as arginine-rich proteins of a relatively low molecular weight that are associated with nucleic acids. Protamines can be obtained in quantity from the sperm heads of certain fish such as salmon or herring by methods known in the art. Protamines can be obtained from Sigma Chemical Co. under the tradename Protamine or Sperm Nuclei (crude form).

Chitosan is made by the partial deacetylation of chitin, a polysaccharide obtained from certain fungi and the exoskeletons of arthropods. Chitosan is chemically identical to modified cellulose in which the C-2 hydroxyl groups have been replaced with primary amine functions.

The positively charged chemical agent of this embodiment is preferably of a size small enough and of optimum steric structure when dissolved in the medium to enter and accumulate in the polymeric pores of the lens bulk matrix such that the ionic charges in the lens will be substantially neutralized at equilibrium as a result of the positively charged agent forming ion pairs with the negatively charged ions of the lens.

It is possible that the precursor chemical agent could be in a form (such as a solid) wherein it is not of the proper size or steric structure, yet when the precursor agent is delivered to the working solution it disassociates or changes sterically in its tertiary or quaternary structure into the actual chemical agent which is of the proper size, shape and charge.

Preferably, the chemical agent possesses a molecular weight ranging from about 100 to about 70,000. More preferably, the chemical agent should have a molecular weight and steric structure that is optimum for penetrating the pores. For example, the chemical agent should have a molecular weight of not less than about 100 in order to penetrate the pores of the lens more easily and neutralize the charges of the lens more quickly. Conversely, if the chemical agent has a molecular weight greater than 70,000, it may be too large to enter the pores of the lens matrix and neutralize the charge of the lens.

If the chemical agent is only slightly smaller than the pore size of the lens polymers, the lens must be soaked for a longer period of time in order for the chemical agent to neutralize the charge associated with the lens. Desorption of such chemical agents will be slow due to the reduced degrees of freedom in the matrix pore, prolonging the time period of effective prevention of deposition of tear proteins. Thus, an optimum molecular weight between 100 and 70,000 exists for each candidate chemical entity that constitutes a compromise of shortest possible treatment time and longest possible time of effective prevention of protein deposition.

Examples of this type of molecule are basic proteins and basic polypeptides such as protamine and polyarginine, both of which have an average charge density greater than the average charge density of lysozyme, the most basic tear protein. Another example is the basic carbohydrate chitosan, which is also positively charged at physiological pH's of 7 to 8.

Preferably the chemical agent of the present invention absorbs more rapidly and/or less reversibly into the lens matrix than lysozyme so that the lysozyme which penetrates and adheres to the matrix is displaced by the



chemical agent and/or is prevented from accumulating on the lens matrix and surface after the treatment process and during the lens wear period.

Preferably the chemical agent is dissolved in an aqueous working solution at a pH ranging from about 6 to about 8.5. More preferably, the chemical agent is dissolved in the solution at pH of 7.4.

The solution of the present invention may be a buffered saline solution, artificial tear solution (described hereinafter), contact lens disinfection solution or some other appropriate vehicle which is biocompatible with the eye or is rendered so by the end of the regimen time period. In addition to the chemical agent, the solution of the present invention may also include ophthalmically acceptable additives such as saline, buffers, preservatives, wetting agents, lubricating agents and/or surfactants, all of which are well known in the art. Further, the solution of the present invention may include disinfecting agents. Examples of disinfecting agents which may be used include, but are not limited to, polyquaternary amines, e.g., Croquat™ L which is commercially available from Croda, Inc., biguanides, and polymeric biguanides such as polyhexamethylene biguanide, available as Cosmocil® CQ from ICI Americas, peroxide and water soluble cationic polymers (WSCP). WSCP is available from Buckman Laboratories, Inc. and are described in U.S. Patent No. 4,250,269, which is incorporated herein by this reference.

Therefore, the solution can be preserved as a soaking solution or as part of a disinfecting solution.

Moreover, the chemical agent can be delivered in a variety of forms including tablet, powder, granules, solution or spray. Such delivery vehicles may contain other ingredients well known in the art so long as they do not affect the chemical agent's function. Such additives include those previously noted as well as fillers, effervescent, biocides and other antimicrobial agents.

Preferably, the lens is contacted with the solution for a period of time such that equilibrium favors desorption of the lysozyme. The desorbed lysozyme is then found solvated in the working solution.

The amount or presence of protein deposits on the lens surface and/or in the lens matrix can oftentimes be determined visually (naturally or with the aid of a magnifying glass) and by the degree of comfort experienced by one wearing the lens. UV spectroscopy or microscopy may also be used to more accurately determine how much protein has been deposited on and in the lens.

It is preferable to soak the lens in about 2.0 to about 20.0 mL of the solution of the present invention for at least about ten minutes, and more preferably from about ten minutes to about six hours. It should be recognized that the amount of time the lens is to be soaked is inversely proportional to the concentration of the chemical agent contained in the solution. For example, by increasing the concentration of the chemical agent in the solution, the soaking time of the lens will be decreased. The soaking time may also depend upon the particular chemical agent being used and the type of lens being soaked.

Generally, the magnitude of the concentration of the chemical agent and the soak time will depend upon, in addition to the molecular weight range of said chemical agent, the amount of lysozyme sorption (adsorption and/or absorption) and the degree of lysozyme attraction to the lens material, as well as the recommended regimen for the user's lenses. It is possible that it may be necessary for the soaking to be repeated several times until the amount and/or the rate of accumulation of lysozyme on and/or in the lens has been appreciably reduced.

Preferably the solution of the present invention contains an effective amount of the chemical agent, i.e., an amount effective to substantially reduce the presence and/or the formation and accumulation of protein deposits on and/or in the lens after a recommended regimen.

More specifically, it is preferred that the working solution contain about 0.01% to about 5.0% by weight of the chemical agent. More preferably, the solution of the present invention contains about 0.1% to about 1.0% by weight of the chemical agent.

It is preferred to soak the lens in the solution at room temperature. Although it may be possible to gently heat the solution, if the solution is more strongly heated, it is possible that the lysozyme may denature and eventually adhere to the lens even more strongly than before the treatment.

It is also preferable that the solution of a positively charged protein preventor of the present invention be used to pretreat new contact lenses, that is, lenses that have never been worn before. For example, a contact lens may be prepackaged in the solution. Pretreating a contact lens in this solution will preferably allow the positively charged chemical agent to be sorbed by the lens, including in the lens matrix, such that the [lens/agent] complex is favored in the environment where the lens is exposed to lysozyme, e.g., in the eye. As a

result, when the contact lens is first placed in the eye, the lysozyme in the eye will preferably have fewer sites to which to bind.

5 A lens swelling treatment may be performed in order to reduce the amount of proteins that may adhere to the lens surface and matrix. By making the solution of the present invention hypotonic and contacting the lens in this solution, the lens will appreciably swell and the pores of the matrix will expand, thereby accelerating and facilitating the rate at which the chemical agent binds to the negatively charged sites of the lens. The lens should not be excessively swelled since excessive swelling may permanently damage the lens and may cause the lysozyme to migrate deeper into the small polymeric pores of the matrix. Such hypotonic solution may be formed, for example, by contacting the chemical agent of this embodiment with water. It is preferable that the hypotonic solution contain 0.0% to about 0.6% and more preferably 0.4% by weight NaCl.

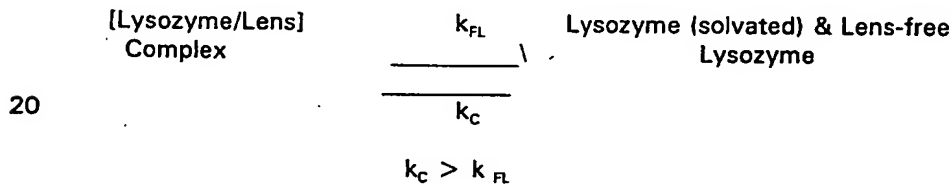
10 Instead of soaking the lens in the solution of the present invention, the solution may be sprayed, dropped or rubbed directly onto the surface of the lens before the lens is placed on the eye. By using this method of contacting the solution with the lens, it is preferable but not necessary to subsequently rinse the lens with an ophthalmically acceptable rinse solution. Instead, the tear itself will help wash away lysozyme which has been desorbed from the lens.

15 If the solution is to be contacted with the lens while the lens is in the eye, it is preferable that the solution does not contain more than 1.0% by weight of the chemical agent since any amount greater than 1.0% may be toxic to the eye. If the solution should contain less than about 0.1% by weight of the chemical agent, the process of neutralizing the charge of the lens, generally, may take too long or may not be effective at all. On the other hand, if the lens has a low ionicity, it may be possible to effectively neutralize the charge of the lens by soaking it in a solution containing less than 0.1% by weight of the chemical agent.

20 In sum, by contacting a contact lens with the solution of the present invention, the positively charged ions of the chemical agent in the solution are used to neutralize the negatively charged ions of the lens material. As a result of this electrostatic interaction, the electrostatic interaction between the lysozyme and the lens material is preferably substantially reduced and/or

completely eliminated, thus lowering the primary interactive force responsible for incipient deposition of lysozyme on and/or in the lens.

Lysozyme is the major tear constituent involved in the formation of deposits and lens soils on hydrophilic contact lenses, especially Group III lenses (low water/ionic lens polymers) and Group IV (high water/ionic lens polymers) lenses. Since lysozyme is positively charged at physiological pH and at pHs encountered with lens care products (pH about 7.0 to 8.0), and contact lenses containing methacrylic acid as a copolymer, i.e., Group III and Group IV lenses, are negatively charged under these same conditions, there is formed an electrostatic attraction between the lens material and the lysozyme. With reference to the following equilibria, the typical electrostatic attraction between the lens material and the lysozyme favors an equilibrium of higher concentration of the protein on the lens than in a medium such as a tear or lens care solution and, thus, results in the formation and accumulation of lysozyme on and/or in the lens.



For example, Group IV lens materials have a pore size sufficient to accommodate the intrusion and accumulation of lysozyme within the lens. Even though the deeper migration of lysozyme into the lens bulk matrix is a slower process than surface accumulation, protein deposits imbedded in the matrix of a lens are less reversibly bound and are more difficult to remove than proteins deposited on the surface of the lens.

By using the chemical agent of the present invention to increase  $k_{FL}/k_c$ , the solution of the present invention becomes more effective at facilitating inhibiting the uptake of lysozyme and reducing the formation of lysozyme deposits on and in the lens.

In another embodiment of the present invention, the formation of protein deposits on and in a hydrophilic lens may be reduced and inhibited by, first, placing the lens in a hypotonic solution for a period of time sufficient to cause the lens to swell and the pores of the matrix to expand and then contacting the lens with a chemical agent selected from the group consisting of chloride salts,

chlorite salts, salts of ethylenediaminetetraacetic acid (EDTA), cysteine and mixtures thereof.

5 The amount of lens swelling depends upon the lens type. The lens, however, should not be swelled excessively because excessive swelling may permanently damage the lens. Further, if the lens is swelled too much, the lysozyme may migrate further into the small matrix pores. This may make it more difficult for the lysozyme to be removed from the lens matrix since lysozyme is less reversibly bound the deeper it gets imbedded in the lens.

10 Preferably, the lens should be soaked in the hypotonic solution for a period of time ranging from about one minute to about thirty minutes, depending on the type of lens being swelled.

The solution used in connection with this embodiment of the method of the present invention may be water, a buffered saline solution, an artificial tear solution or a contact lens disinfection solution, so long as it is hypotonic.

15 Preferably, the solution contains from 0 to up to about 0.6% by weight sodium chloride in order to create an environment where the osmotic pressure within the lens is lower than the osmotic pressure of the surrounding solution, thus creating an environment sufficient to cause the lens to swell and its pores to expand.

20 The hypotonic solution preferably possesses a pH ranging from about 1 to about 13 in order to reduce the charge of the lysozyme (high pH) or lens material (low pH) and contribute to the swelling (high pH) or shrinkage (low pH) of the lens. More preferably, the pH of the hypotonic solution ranges from about 9 to about 12 for a period of time ranging from 1 minute to 30 minutes with a final pH of about 7.4 in order to help neutralize the charge of the lysozyme or from about 3.5 to about 2 for a period of time ranging from 1 minute to 30 minutes with a final pH of about 7.4 in order to help neutralize the charge of the lens. By neutralizing the charge of the lysozyme or lens material, the lysozyme will possess a lower affinity for the lens matrix and, thus, be more easily desorbed from the matrix. If the pH of the solution is greater than about 12 or lower than about 2, the basicity or acidity of the solution may damage the lens by breaking the ester bonds in the lens material.

30 After the lens has swelled and the pores have become dilated, a negatively charged chemical agent and any necessary pH neutralizing agent is released (via a delayed release mechanism) into the hypotonic solution. The chemical agent and pH neutralizing agent are present in the solution in an

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amount sufficient to adjust the pH to the physiological range (generally in the range of 6.5 to 8.5) and to cause the hypotonic solution to become isotonic or hypertonic and to also increase the ionic charge density/strength of the solution in order to simultaneously facilitate desorption of the protein deposits from the surface and matrix of the lens. The change in the osmotic pressure of the solution will cause the lens, while in the solution, to shrink and the pores of the lens matrix to constrict.

The chemical agents of this embodiment consist of relatively small molecules. For example, one of the largest molecules of this group of negatively charged chemical agents is EDTA which has a molecular weight of about 233. These molecules compete with the lens material to bind to the lysozyme in the matrix. After the chemical agent is bound to the lysozyme in the matrix, the agent/lysozyme complex is removed from the lens as a result of the inherent egress of water out of the lens. The lysozyme, being more soluble in the higher ionic strength working solution and less soluble in the lens matrix, diffuses out and away from the pores of the matrix into the more stabilizing environment of the solution.

Chloride salts which may be used in this embodiment include, but are not limited to, NaCl, KCl and  $\text{CaCl}_2$ . It is preferred that the solution contain at least about 0.9% by weight chloride salt up to the solubility limit of the chloride salt in the solution. It is more preferable that the solution contain from about 0.9% to about 2.0% by weight chloride salt.

If a chlorite salt is used in this embodiment of the present invention, it is preferred that the solution contain at least about 0.05% up to about 2.0% by weight chlorite salt in such solution along with other more common salts, such as chloride and/or phosphate salts to make the solution about isotonic. More preferably the solution contains from about 0.1% to about 1.0% by weight chlorite salt. In the present invention, the preferred chlorite salt is  $\text{NaClO}_2$ .

If a salt of EDTA is selected as the chemical agent of this embodiment, it is preferable that the solution contain at least about 0.05% by weight up to about 2% of the salt of EDTA in the solution. More preferably the solution contains from about 0.1% to about 1.0% by weight EDTA along with other more common salts and buffers.

When using cysteine, it is preferred that the solution contains at least about 0.1% by weight cysteine up to about 3.0% by weight cysteine in such

solution. More preferably the solution contains from about 0.5% to about 2.0% by weight cysteine.

Further, it is preferable that the chemical agent, when added to the hypotonic solution, have a delayed or time-release coating in order to allow  
5 more time for the lens to swell and facilitate and maximize desorption of the protein before the lens and the pores of the matrix shrink back to their previous, desired size prior to having been placed in the hypotonic solution.

Even though the chemical agent of this embodiment may be directly added to the hypotonic solution in the form of a solution, in order to add the  
10 chemical agent to the hypotonic solution in a delayed-release manner it is preferred that the chemical agent be present in the form of a tablet, pill, capsule, powder or the like which includes a coated portion. For example, a tablet may have a core containing the chemical agent and thereupon placed a barrier component coating to delay release of the chemical agent present in the  
15 core.

If the solution to which the agent is added has a pH higher or lower than physiological pH, it may be desirable to add an additive to the core in order to maintain and/or bring the pH of the working solution to about 7.0 to about 8.0. Lysine dihydrochloride, tartaric acid, citric acid, sodium carbonate and mixtures  
20 thereof are examples of additives which may be used to help neutralize the pH of the solution.

The barrier component coating can act to delay the release of the chemical agent from the core portion, preferably, for a period of time sufficient to reduce the accumulation of lysozyme at the surface of the lens and in the  
25 lens matrix.

The delayed-release of the chemical agent into the solution may be accomplished in any one of a number of suitable ways, a number of which are conventional and well known in the art. A barrier component may consist of a slowly dissolving coating material.

Barrier components suitable as coatings include water soluble vinyl  
30 polymers such as polyvinyl pyrrolidone, polyvinyl alcohol and polyethylene glycol; water soluble protein, polysaccharide and cellulose derivatives such as methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, alginic acid and its salts and other derivatives, and the  
35 like and mixtures thereof.

The amount of barrier component used is not critical in the present invention provided that such barrier component functions as described herein.

A preferred delayed-release coating or barrier component is derived from a mixture comprising polyvinyl alcohol and a water soluble soaking component.

5        Alternatively, instead of providing a tablet, for example, having a core containing the chemical agent, the core may include only the additive, and the additive may be covered with a mixture of the chemical agent and the barrier component. Also, the tablet may be comprised of a core which includes the pH neutralizing additive. This core may then be covered with the barrier  
10       component, and the barrier component, in turn, may be covered by the chemical agent which is also covered with another layer of the barrier component.

      The lens is soaked in the solution of the negatively charged agent for a period of time sufficient to potentiate the desorption of the lysozyme from the  
15       lens material by presenting a more thermodynamically favorable environment in the solution than as exists for the protein in the lens matrix and on its surface. This process of protein desorption from the lens is further enhanced by the favorable kinetics provided by the increased degrees of freedom of the sorbed protein from the lens swelling process. As the lens pores return to their original  
20       size, the rate of protein desorption again decreases. Thus, the process may need to be repeated several times to substantially rid the lens of lysozyme. Preferably, the lens is soaked in the solution for a period of time ranging from about ten minutes to about six hours.

      The goal is to enhance the rate of diffusion of the protein from the lens  
25       material by reducing the affinity of the lysozyme for the lens material and increasing the affinity of the lysozyme protein for the negatively charged chemical agent in the working solution.

      In addition to the chemical agent, the solution of this embodiment may include ophthalmically acceptable additives such as saline, buffers,  
30       preservatives, wetting agents, lubricating agents and/or surfactants, all of which are well known in the art. Further, the solution of this embodiment may include disinfecting agents, e.g., peroxide, polyquaternary amines, biguanides and WSCP.

      In yet another embodiment of the present invention, a larger sized  
35       negatively charged chemical agent having a high charge density is used to inhibit and/or reduce the amount of protein lysozyme present on the surface



and/or in the inner bulk matrix of a contact lens. The method of this embodiment comprises first placing the lens in a hypotonic solution for a period of time sufficient to cause the lens to swell and the pores of the matrix to expand. Again the lens should not be swelled excessively since excessive swelling may damage the lens.

Preferably, the solution contains from 0 to up to about 0.6% by weight sodium chloride in order to create an environment where the osmotic pressure within the lens is lower than the osmotic pressure of the surrounding solution, thus creating an environment sufficient to cause the lens to swell and its pores to expand.

The hypotonic solution preferably possesses a pH ranging from about 1 to about 13 in order to reduce the charge of the lysozyme (high pH) or lens material (low pH) and contribute to the swelling (high pH) or shrinkage (low pH) of the lens. More preferably, the pH of the hypotonic solution ranges from about 9 to about 11.5 in order to help neutralize the charge of the lysozyme or from about 2 to about 3.5 in order to help neutralize the charge of the lens. By neutralizing the charge of the lysozyme or lens material, the lysozyme will possess a lower affinity for the lens matrix and, thus, be more easily desorbed from the matrix. If the pH of the solution is greater than about 13 or lower than about 1, the basicity or acidity of the solution may damage the lens by breaking the ester bonds in the lens material.

After the lens has swelled, it is then contacted with a solution comprising an effective amount of a negatively charged chemical agent selected from the group consisting of alginic acid (a linear polymer of  $\beta$ -(1 $\rightarrow$ 4)-D-mannosyluronic acid and  $\alpha$ -(1 $\rightarrow$ 4)-L-glucosyluronic acid residues), propylene glycol alginate, xanthan gum (polysaccharide gum composed of D-glucosyl, D-mannosyl and D-glucosyluronic acid residues and differing portions of O-acetyl and pyruvic acid acetal produced by bacterium *xanthomonas campestris*), hyaluronic acid, chondroitin sulfate and mixtures thereof, for a period of time sufficient to reduce and inhibit the formation of protein deposits on and in the lens. For purposes of this embodiment, an effective amount is an amount such that after contacting the lens with the solution the chemical agent facilitates desorption of the proteins from the lens. Further, the bulk solution osmotic pressure is hypotonic and, at the same time, the osmotic pressure of the solution outside the lens matrix is higher than the osmotic pressure of the solution inside the lens matrix because of the inability of the large agent molecule to penetrate

into the pores of the lens. The combination of overall low osmotic pressure of the bulk solution and the osmotic pressure differential between the bulk solution and the lens matrix has the net effect of swelling the pores of the lens and simultaneously potentiating the egress of protein from the lens matrix into the more stabilizing environment of the bulk solution. A low molecular weight salt (e.g., sodium chloride) may then be released into the solution to bring the osmotic pressure of the bulk solution to near isotonic.

Even though the solution can be applied directly to the lens while the lens is worn (if the solution is slightly hypotonic), it is more desirable to soak the lens in the solution for a period of time ranging from at least about ten minutes to about six hours, depending upon the lens regimen.

The solution of this embodiment may be a buffered saline solution, artificial tear solution, contact lens disinfection solution or some other appropriate vehicle which is biocompatible with the eye or is rendered so by the end of the treatment period.

The negatively charged chemical agent of this embodiment is larger than the pore size of the lens material; i.e., the chemical agent is unable to migrate into the polymeric pores of the lens matrix. It is preferred that the negatively charged chemical agent has a molecular weight ranging from about 50,000 to about 1,000,000 daltons. More preferably, the negatively charged chemical agent has a molecular weight ranging from about 70,000 to about 150,000. If the chemical agent of this embodiment has a molecular weight of less than about 50,000, it may diffuse into the matrix of the lens and combine with lysozyme in the matrix, causing increased steric hindrance for the migration of lysozyme out of the lens pores. If the molecular weight of the chemical agent is greater than about 1,000,000, it may make the solution too viscous and unable to effectively desorb the lysozyme from the lens.

Preferably, the solution contains from about 0.1% to about 5% by weight of the chemical agent. More preferably, the solution contains from about 0.5% to about 2% by weight of the chemical agent.

In addition to the chemical agent, the solution of this embodiment may include ophthalmically acceptable additives such as saline, buffers, preservatives, wetting agents, lubricating agents and/or surfactants, all of which are well known in the art. Further, the solution of this embodiment may include disinfecting agents, e.g., peroxide, polyquaternary amines, biguanides and WSCP.

Also, it is preferable that the solution of this embodiment be agitated or sonicated either intermittently, continuously or at a strategic time during the treatment process in order to prevent the possible formation of film on the lens which may be caused by the alginate, for example, reacting with the protein.

5 For example, an additive such as an effervescent may be added to the solution in order to agitate it and disperse or prevent the formation of the resulting film on the lens surface. As another example, the catalytic decomposition of hydrogen peroxide to oxygen plus water may be used to produce sufficient turbulence to disperse or prevent the formation of the resulting film on the lens  
10 surface.

The mechanism of the method of this embodiment involves creating and maintaining for an effective period of time a solution environment where the ionic strength of the chemical agent in the solution is greater than the ionic strength within the lens matrix. This is a result of the chemical agent being  
15 excluded from the lens material due to its size and the chemical agent substantially increasing the total ionic strength of the solution. The tear proteins or lysozyme, being more soluble in the higher ionic strength solution and less soluble inside the lens matrix, diffuse out and away from the lens pores into the more stabilizing environment of the solution. Once outside the  
20 lens, the protein or lysozyme is neutralized by ionic pairing with the chemical agent. In sum, the solution of this embodiment facilitates reversal of sorption of lysozyme from the lens into the solution. Preferably, a low molecular weight salt, such as sodium chloride, is introduced into the solution (by e.g., a delayed release mechanism) toward the end of the regimen period in order to bring the  
25 tonicity inside the lens matrix up to near isotonic. This is needed to insure that the lens parameters will return to the original values before the lens is placed into the eye. An example of this embodiment is a peroxide solution containing an alginate salt of molecular weight greater than 50,000 at a concentration of 0.5% to 1% to which is added a coated tablet containing sodium chloride and  
30 catalase in the tablet core and sodium alginate and/or hydroxypropyl methyl cellulose in the tablet coating. The tablet and lens are placed into the solution at the same time. Alternatively, a double coating may be employed whereby dissolution of the first coating releases catalase to decompose the hydrogen peroxide, and dissolution of the second coating releases the sodium chloride for  
35 tonicity adjustment.

The following two in vitro methods of depositing lysozyme proteins on the surface and in the inner bulk matrix of a contact lens were used to illustrate in vivo adsorption of the proteins. Group IV hydrophilic contact lenses were used for both methods. These examples are in no way intended to limit this invention.

The surface protein deposit for each lens was evaluated according to the following lens deposit classification system: Class I - deposit is not visible with a 7x to 10x magnifier; Class II - deposit visible with a 7x to 10x magnifier; Class III - deposit visible when dry to the unaided eye; and Class IV - deposit visible when wet or dry to the unaided eye. This entire procedure was repeated for each of the chemical agents listed below in Table 1.

The analytical methods for comparing the lenses after treatment with the test and control solutions are specific for protein. A first-derivative UV spectroscopic technique that is specific for lysozyme was utilized for comparing the lenses with respect to total (matrix plus surface) lysozyme content. This method is based on the derivative response between 289 nm and 293 nm that results from a shoulder at 290 nm in the normal absorption spectrum of lysozyme. The peak-to-peak response in the derivative spectrum is directly proportional to the lysozyme content of the lens, assuming that all test and control lenses have the same dimensions.

The surface analysis of lenses was accomplished by attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. The effective depth of penetration of the lens surface by the evanescent radiation is approximately 1 micron using a zinc selenide crystal having a 45° angle of incidence. A single-reflection, horizontal-surface accessory (from Harrick), with a metal plate and pressure clamp to hold the lens against the element surface was used. The absorbance of the amide II band at ~ 1550 wavenumbers, after spectrally subtracting water from the lens spectrum, was used for comparing the test and control lenses with respect to the protein content. The results, set forth in Table 1 below, for either the total lysozyme (UV method) or surface protein (ATR-FTIR) were calculated as follows:

$$\left[ \frac{\text{test response}}{\text{control response}} \times 100 \right] - 100 = \% \text{ difference from control}$$

Note that negative % difference indicates enhanced protein removal and/or decreased protein deposition by the test solution. Zero indicates no difference from the control; and positive % difference means that the control solution exhibits more protein removal and/or deposit inhibition than the test solution.

5

#### METHOD I - LENS CYCLING

In this method of protein deposition and measurement, Acuvue lenses (Group IV lens polymers) were used. In this method, three different kinds of lysozyme coating solutions were prepared: an FDA Artificial Tear Model Solution, a Full Tear Formulation and the "Solution of Interest". For purposes of this invention, Solution of Interest is defined as the FDA Artificial Tear Model Solution (see below) with the chemical agent (see Table 1 below) added to it to give a final concentration of 1 mg/mL wherein the pH of the solution was adjusted to 7.3 - 7.4 with 1N NaOH or 1N HCl.

15

FDA Artificial Tear Model Solution was prepared using the following ingredients and preparation procedure:

TABLE 1  
FDA Artificial Tear Model Solution

20

<u>Ingredient</u>	<u>mg/mL</u>
Lysozyme, egg white	1.20
Albumin, bovine	3.88
25 Globulins, human	1.61
Sodium chloride	9.00
Calcium chloride, anhydrous	0.11
(Calcium chloride, dihydrate) <sup>1</sup>	0.15
Sodium phosphate, dibasic, heptahydrate	0.28
30 (Sodium phosphate, dibasic, anhydrous) <sup>2</sup>	0.15

#### Preparation Procedure

- Dissolve proteins in D.I. water
- Add remaining ingredients in order listed
- 35 • Adjust pH to 7.0 with 1N NaOH or 1N HCl

<sup>1</sup> Calcium chloride, anhydrous may be substituted for calcium chloride, dihydrate.

<sup>2</sup> Sodium phosphate, dibasic, anhydrous, may be substituted for sodium phosphate, dibasic, heptahydrate.

TABLE 2  
Full Tear Solution

	<u>Tear Component</u>	<u>Source</u>	<u>Concentration</u> <u>(mg/mL)</u>
5			
	1. Lysozyme	Chicken Egg White	1.9
	2. Albumin	Human Serum	0.2
10	3. Gamma Globulins (IgG + ...)	Human Serum	0.1
	4. Lactoferrin	Bovine Milk	1.6
	5. Mucin	Bovine Submaxillary	0.15
	6. $\alpha_1$ -Acid Glycoprotein	Bovine Serum	0.5
15	7. Sodium Chloride		3.0
	8. Potassium Chloride		0.9
	9. Calcium Chloride		0.04
	10. Chloride		4.9
	11. Sodium Bicarbonate		1.0
20	12. Dihydrogen Phosphate $\text{NaPO}_4$ , anhydrous		0.07
	13. Lactic Acid (Sigma)		0.27
	14. 3-(N-Morpholino) Propanesulfonic acid		4.18
	15. Oleic Acid Propyl Ester		0.012
	16. Triolein (1,2,3-Tri-[(cis)-9-octadecenoyl] glycerol)		0.016
25	17. Dicaproin ( $\text{C}_{15}\text{H}_{28}\text{O}_5$ ) mixture of isomers		0.0032
	18. Linalyl Acetate (Aldrich)		0.02
	19. Cholesterol Linoleate		0.024
	20. Cholesterol		0.0016
30	21. Undecylenic Acid, Sodium salt (Undecanoic Acid, Na salt)		0.003

First, a test lens was inverted and soaked, concave up, in phosphate buffered saline solution overnight at room temperature. This lens was then soaked for one hour in a Solution of Interest comprising one of the chemical agents selected from the list of chemical agents set forth in Table 3, below. The lens was subsequently soaked for four more hours in either the FDA Artificial Tear Solution or Full Tear Solution. The lens was once again soaked in the Solution of Interest for one hour at room temperature. Thereafter, the lens was soaked in the FDA Artificial Tear Solution at 37°C. (2 cycles).

A control lens was soaked either in the FDA or Full Tear solution at pH of about 7.3 - 7.4, without the chemical agent present.

Lens matrix protein was first measured by derivative UV spectroscopy (as described above) after 2, 4 and 6 cycles. Lens surface protein was measured by ATR-FTIR spectroscopy (also described above).

Competitive inhibition of lysozyme deposition was observed in the lens matrix. The lenses were stained with Oil Red O to see if lipid deposits could be assessed, but it was found that the stain was inferior for quantitative differentiation. UV and ATR-FTIR spectroscopy results are expressed as % difference from the control.

The same method was repeated for each other test chemical agent listed below in Table 3, using a separate lens for each experiment.

In this method, polyarginine and protamine were the two chemical agents most effective in reducing protein formation in the matrix, with sodium alginate also functional.

TABLE 3  
Percent Difference From Control for Lenses Treated by Cycling and Sorption Models (N=3)

Tear Type Analysis Zone	LENS CYCLING								SORPTION		
	FDA Tear				Full Tear				FDA Tear		
	Matrix (UV)				Surface				Matrix (UV)		
Days of Treatment	1	2	3		1	2	3		1	2	3
CMC	0	-6	-6	+18	-2	-2	+2	+18	-4	-11	+5
Glutathione	+2	-4	-5	-14	-5	-2	+1	-12	0	-2	+2
PVA	+11	-6	-7	-6	-	-	-	-	-1	-1	+7
Polyarginine	-88	-93	-93	-31	-69	-82	-83	-48	-90	-93	-91
Protamine	-74	-86	-86	-8	-69	-81	-93	-25	-84	-87	-86
HPMC	+6	-5	-7	-29	-5	-3	-1	-38	-2	-3	-5
Polylysine	-16	-6	-2	+12	-	-	-	-	-5	-13	-16
Alginate, Sodium	-1	-15	-14	-17	-6	-6	0	-19	-22	-24	-14
Cysteine	-5	-6	-10	-13	+2	+1	0	+6	+6	+3	+10
Arginine	0	0	+3	+29	-	-	-	-	-8	-12	-18
EDTA	-	-	-	-2	-1	+3	-16	-	-	-	-
Bendazac	+1	+2	-1	+33	+11	-1	-7	-7	-	-	-
Celluvisc™ "lite"	-	-	-	-	0	+2	+6	-44	-	-	-

\*ATR-FTIR Analysis  
-No Data

## METHOD II - SORPTION

The sorption method of protein deposition and measurement was performed using Acuvue lenses.

5 FDA Artificial Tear Solution, as shown above, was prepared and used as a control solution. A Solution of Interest was prepared by adding one test chemical agent selected from the list of chemical agents in Table 3 to the FDA Artificial Tear Solution to give a final concentration of 1mg/ml. The pH of this solution was then adjusted to about 7.3 to 7.4 with 1N NaOH or 1N HCl.

10 One lens was soaked in the control solution and another lens was soaked in the Solution of Interest for 4, 8, 24, 48 and 72 hours each. Lens matrix proteins were measured first by derivative UV spectroscopy and lens surface proteins were measured by ATR-FTIR spectroscopy (see above) after having been soaked for 4, 8, 24, 48 and 72 hours.

15 This method was repeated using each of the remaining test chemical agents listed in Table 3, above. The results of this method, as shown in Table 3 above, are expressed as % different from the FDA artificial tear solution control.

20 Having thus described the exemplary embodiments of the present invention, it should be noted by those skilled in the art that the within disclosures are exemplary only and that various other alternatives, adaptations and modifications may be made without departing from the spirit and scope of the present invention. Accordingly, the present invention is not limited to the specific embodiments illustrated herein, but is only limited by the following  
25 claims.



**What is claimed is:**

1. A method of reducing the formation and inhibiting the uptake of protein deposits on the outer surface and/or in the inner bulk matrix of a hydrophilic contact lens, comprising:  
5                   contacting a contact lens with a chemical agent selected from the group consisting of protamines, polyarginine, polylysine, chitosan and its salts and derivatives, and mixtures thereof.
2. The method as defined in claim 1 wherein there is present by weight 0.01% to 5.0% of the chemical agent.
3. The method as defined in claim 1 wherein the chemical agent has a molecular weight ranging from 100 to 70,000.
4. The method as defined in claim 1 further including adding the chemical agent to an aqueous solution wherein the solution has a pH ranging from 6 to 8.5.
5. The method as defined in claim 4 wherein the lens is contacted with the solution while the lens is in the eye.
6. The method as defined in claim 4 wherein prior to contacting the lens with the solution, the lens is contacted with a hypotonic solution for a period of time to appreciably swell the lens.
7. A method of reducing the formation and inhibiting the uptake of protein deposits on the outer surface and/or in the inner bulk matrix of a hydrophilic contact lens comprising:  
5                   contacting the contact lens with a solution at physiological pH containing at least 0.1% by weight of a positively charged and water soluble chemical agent selected from the group consisting of protamines, polyarginine, polylysine, chitosan and mixtures thereof, wherein the chemical agent has a molecular weight ranging from 100 to 70,000, and wherein the solution has a pH ranging from about 6 to about  
10                  8.5.

8. The method as defined in claim 7 wherein the solution is hypotonic.
9. For use in a contact lens solution, a composition for reducing the formation and inhibiting the uptake of protein deposits on the outer surface and/or in the inner bulk matrix of a hydrophilic contact lens, the composition containing:
- 5        an effective amount of a chemical agent selected from the group consisting of protamines, polyarginine, polylysine, chitosan and mixtures thereof.
10. The composition as defined in claim 9 wherein there is present by weight 0.01% to 5.0% of the chemical agent.
11. A method of reducing the formation and inhibiting the uptake of protein deposits on and/or in a hydrophilic contact lens wherein the lens has an outer surface and an inner bulk matrix with polymeric pores, the method comprising the steps of:
- 5        placing the lens in a hypotonic solution for a period of time sufficient to cause the lens to swell and the pores of the matrix to expand;
- 10        adding a negatively charged chemical agent to the solution such that the solution possesses an osmotic pressure sufficient to cause the lens and the pores of the matrix to constrict, and wherein the chemical agent is present in an amount sufficient to cause desorption of the protein deposits from the surface and/or matrix of the lens; and
- 15        soaking the lens in the solution having the chemical agent for a period of time sufficient to appreciably reduce the formation of protein deposits on or in the lens.
12. The method as defined in claim 11 wherein the chemical agent is selected from the group consisting of chloride salts, chlorite salts, sodium salts of ethylenediaminetetraacetic acid, cysteine and mixtures thereof.
13. The method as defined in claim 11 wherein the solution at end of regimen contains at least 0.9% by weight chloride salt.

14. The method as defined in claim 11 wherein the solution at end of regimen contains at least 0.1% by weight chlorite salt.
15. The method as defined in claim 11 wherein the solution at end of regimen contains at least 0.05% by weight sodium salts of EDTA.
16. The method as defined in claim 11 wherein the solution contains at least 0.1% by weight cysteine.
17. The method of claim 11 wherein the solution at end of regimen contains sufficient salts to render the solution substantially isotonic.
18. A method of cleaning a contact lens, the method comprising the steps of:  
placing the lens in a hypotonic solution comprising 0.0% to  
0.6% by weight of sodium chloride for a period of time  
sufficient to cause the lens to swell and the pores of  
the matrix to expand;  
contacting the lens in the solution with a negatively charged  
chemical agent selected from the group consisting of chloride  
salts, chlorite salts, ethylenediaminetetraacetic acid sodium  
salts, cysteine and mixtures thereof, the chemical agent being  
present in the solution in an amount sufficient to (a) facilitate  
desorption of the protein deposits from the surface and matrix  
of the lens and (b) change the tonicity of the solution so as to  
cause the lens pores of the matrix to constrict, wherein the  
lens is soaked in the solution having the chemical agent for a  
period of time sufficient to appreciably reduce or inhibit the  
formation of protein deposits on or in the lens.
19. The method as defined in claim 18 wherein the hypotonic solution has a pH ranging from about 2 to about 3.5 for a period of time ranging from 1 minute to 30 minutes and a final pH of about 7.4.
20. The method as defined in claim 18 wherein the hypotonic solution has a pH ranging from 9 to 12 for a period of time ranging from 1 minute to 30 minutes and a final pH of about 7.4.

21. The method as defined in claim 18 wherein the pH is maintained within the range of 6.5 to 8.5 throughout the treatment period.
22. The method as defined in claim 18 wherein the agent is in the form of a tablet having a time-release chemical coating formed about the chemical agent.
23. A method of reducing the formation and inhibiting the uptake of proteins on and/or in a hydrophilic contact lens, the method comprising the steps of:  
placing the lens in a hypotonic solution for a period of time sufficient to  
cause the lens to swell and the pores of the lens matrix to expand;  
5 contacting the contact lens with an aqueous solution containing a high  
molecular weight, negatively charged chemical agent selected from  
the group consisting of alginic acid, propylene glycol alginate,  
xanthan gum, hyaluronic acid, chondroitin sulfate and mixtures  
thereof; and thereafter  
10 contacting the contact lens with an aqueous solution containing a  
sufficient level of salts and buffers to render the lens bulk matrix  
substantially isotonic with the human tear.
24. The method as defined in claim 23 wherein the solution contains at least 0.1% to 5.0% by weight of the chemical agent.
25. The method as defined in claim 23 wherein the solution is slightly hypotonic and said solution is applied directly onto the contact lens while the contact lens is in the eye.
26. The composition as defined in claim 23 wherein the chemical agent has a molecular weight ranging from 50,000 to 1,000,000.
27. The composition as defined in claim 23 wherein the solution contains 0.1% to 5% by weight of the chemical agent.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 93/11732

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C11D3/22 C11D3/37 C11D3/38 C11D3/384 C11D3/33  
C11D3/34 A61L2/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 C11D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US,A,4 715 899 (CHANDA ET AL.) 29 December 1987 see claims 1,2; example 1 ---	11-13, 16-18
X	WO,A,92 21049 (ALLERGAN) 26 November 1992  see page 6, line 24 - page 12, line 21; claims 1,3,7,8,11,13-18,22-24 ---	11-13, 16-18
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 93/11732

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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